Introduction to OCBQ, DMPQ, and Lot Release

CBER 101

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Division of Manufacturing and

Product Quality

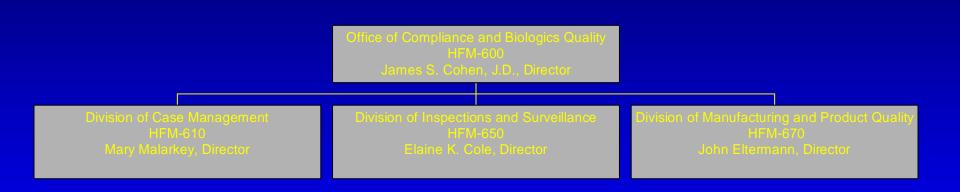
Items to be Covered

- OCBQ overview
- Divisions and scope of responsibilities
- Focus on DMPQ responsibilities
 - Reviews
 - Inspections
 - Meetings
 - Lot release
 - Policy issues/Guidance documents
- Future activities and new directions

Office of Compliance and Biologics Quality

- OCBQ has many diverse and cross-cutting functions
- OCBQ has responsibilities for issues throughout the product life cycle, from IND to post marketing surveillance
- OCBQ works closely with the product offices
- OCBQ serves as CBER's interface with ORA and districts

OCBQ Organization Chart



Division of Case Management

- Reviews and evaluates compliance action recommendations including suspensions, revocations, Warning letters
- Responsible for the review of export applications
- Blood, plasma, and tissue enforcement actions
- Reviews promotional labeling and advertising

Division of Inspections and Surveillance

- Manages Bioresearch monitoring and complaints for IND products
- Manages the product shortage program
- Reviews Biological Product Deviation Reports
- Coordinates CBER activities with ORA, including Team Biologics
- Develops and updates compliance programs

Division of Manufacturing and Product Quality

- Independent review of manufacturing supplements
- Part of the review team for submissions such as applications, supplements chaired by the product office, INDs, DMFs
- Administer CBER's lot release program
- Administrative handling of the pre-approval/prelicense inspections and leading these inspections
- Active role in policy and guidance development

DMPQ Responsibilities in the Review Process

- DMPQ reviewers may be part of a larger CBER review committee or DMPQ may have sole responsibility for review/approval
- DMPQ is involved with a significant percentage of the total submissions received by CBER
- DMPQ is responsible for reviewing issues in CMC as well as responsibility for the review of the Establishment Description Section
- DMPQ coordinates and leads pre-approval/prelicense inspections

DMPQ Responsibilities in the Review Process

- DMPQ review responsibilities include process control, equipment process capability, process validation issues, and GMP assessments
- DMPQ handles administrative reviews such as licensing issues (corporate name changes, mergers, etc.)
- DMPQ now responsible for CBER's pre-approval inspections (notification to district and projections for fiscal year)

DMPQ Responsibilities in the Review Process

- INDs/DMFs consult reviewers; administratively handles Type V DMFs
- Meetings facility meetings at any stage in the process (IND or BLA) for new or renovated facilities
- Communication at pre-BLA stage is critical

 overview of the facility and production
 schedule

Role as an Inspector (Pre-inspection Preparation)

- Review BLA/BLS to identify inspection issues
- Determine if an inspection is needed (SOPP 8410)
- Act as the Inspection Team Leader
- Contact Firm to coordinate the inspection schedule based on the manufacturing schedule
- Notify the Field District Office

Role as an Inspector

(Factors for Determining the Need for an Inspection)

- CBER SOPP 8410
 - No active U.S. license
 - Time frame of previous inspection
 - Significant cGMP deficiencies during previous inspection
 - Significant manufacturing steps in new areas with different equipment
 - Sufficiently different manufacturing process

Role as an Inspector (Inspection Purpose and Team)

- Purpose of the inspection
 - Determine facility compliance with cGMPs
 - Verify CMC sections with respect to data integrity
 - Review documentation that is not included in the BLA but is part of the overall review of the product
 - Evaluate manufacturing control
- Inspection Team
 - DMPQ Lead inspector
 - Product specialist
 - ORA district field investigator (invited)

Potential Approval Delay Issues

- Process Validation
- Manufacturing consistency
- Equipment and Systems Qualification
- Quality Control Oversight
- Standard Operating Procedures

Meetings with Industry

- Communication is critical do not neglect the manufacturing facility issues during the development and pre-submission phase
- We strongly recommend a meeting to discuss the facilities that are performing manufacturing steps
- Submission and product schedule need to perform a meaningful inspection

DMPQ - Role in Policy Development

- Policy and procedures: members of CBER's coordinating committees
- Work on guidance documents such as:

 - ICH Q7A Aseptic processing
 - facilities and use of spore-formers
- Technical issues such as:
 - Barrier Isolators EM
 - BSE

- sterilization

Introduction to Lot Release

- 21 CFR Part 610, Subpart A
- Sets requirements for each applicable test to be performed by the manufacturer
- States that samples and protocols need to be submitted to CBER
- States that no lots may be distributed unless released by CBER
- Specific tests found in other sections

Lot Release - Overview

- Manufacturing and testing information for each lot of product needs to be reviewed by CBER prior to distribution
- Manufacturers submit lot release protocols and samples
- Some products are exempt from lot release

Final Actions Completed (Releases and Withdrawals)



Lot Release - Overview

- Protocol may be for bulk, concentrates or final container material
- Some products have releases at several stages (release at conc. and final container)
- Some products are released at the bulk stage and used for multiple filling (no final container material is submitted)
- IVDs are released as complete kits*

Lot Release Process

- Samples and protocols submitted to CBER, together or separate
- Information entered into CBER database
- Protocols reviewed by scientific staff to ensure specifications met
- Product samples are available for confirmatory testing
- Protocol package is reviewed by Product Release Branch and the lot is released

Exemptions from lot release

- Manufacturer submits supplement requesting exemption. Criteria announced in July 20, 1993 FR Notice
 - History of lots manufactured
 - Fate of these lots
 - Complaints, corrective actions
 - Description of major process changes
- May 1996 FR Notice: Biotech products exempt

Product lots Submitted in Support of a Supplement

- Some manufacturing changes require lots to be submitted to assess impact on product quality
- Protocols should include the Reference Number
- For PAS, lots not released until approval
- For CBEs or CBE-30s, may be released prior to supplement approval

DMPQ - Future Activities

- Addressing the challenges for licensing products for counter-terrorism and novel therapies
- CBER is reviewing the lot release process from a risk-management viewpoint
- Improvements to the review process, administrative actions to meet PDUFA and MDUFMA goals
- Implementation of the GMP initiatives
- Guidance document development

OCBQ Summary

- OCBQ has many diverse functions that impact on product development, review process, and post-licensure
- OCBQ has many responsibilities beyond the traditional compliance functions
- OCBQ is an integral part of the management and oversight of CBER's products

DMPQ Summary

- Many roles of DMPQ within CBER
- Our responsibilities are an integral part of the review process
- Involved as part of the review team on many CBER submissions
- Lot Release and certain manufacturing supplements – DMPQ lead
- Lead for the preapproval inspections

Summary

- Conducting an inspection as part of the review process is a <u>regulatory requirement</u>
- Critical to communicate with CBER with respect to the facility early in the product development process
- An expedient recommendation of an establishment for licensure is dependent on demonstrating process and facility control and compliance with all other pertinent establishment standards

Contact Information

Reviews/meetings:

HFM-670 (301) 827-3031 (301) 827-3536 fax

Lot release issues

HFM-672

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